

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. DOI: 10.1056/NEJMoa2021680

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.
Supplement to: Feldstein, L.R., Rose, E.B., Horwitz, S.M. Multisystem inflammatory syndrome in U.S. children and adolescents

Table of Contents:

Overcoming COVID-19 Study Group Investigators (Pages 2-4)

CDC COVID Response Team (Page 4)

SUPPLEMENTARY METHODS & RESULTS (Pages 5-7)

SUPPLEMENTARY TABLES (Pages 8-18)

- **Table S1 (Page 8):** Case definition used in this study for multisystem inflammatory syndrome in children (MIS-C)
- **Table S2 (Page 9-10):** Kawasaki disease-like (KD-like) signs evaluated in patients with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 illness
- **Table S3 (Page 11-12):** Definitions used for organ system involvement
- **Table S4 (Page 13):** Clinical characteristics of patients with multisystem inflammatory syndrome in children (MIS-C) by age
- **Table S5 (Page 14):** Demographic, clinical characteristics, and interventions among patients with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 who died
- **Table S6 (Page 15):** Non-cardiovascular complications laboratory, and diagnostic findings in patients with multisystem inflammatory syndrome in children (MIS-C) by age
- **Table S7 (Page 16):** Laboratory value numerators and denominators for *Figure 3: Laboratory markers in patients with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19*
- **Table S8 (Page 17-18):** Comparison of demographics, clinical characteristics, and outcomes of patients with multisystem inflammatory syndrome in children (MIS-C), excluding and including the 27 cases at these centers that were included in the New York Department of Health report.

Overcoming COVID-19 Investigators
(listed in PubMed, and ordered by U.S. State)

The following study group members were all closely involved with the design, implementation, and oversight of the Overcoming COVID-19 study.

Alabama: Children's of Alabama, Birmingham. Michele Kong, MD.

Arkansas: Arkansas Children's Hospital, Little Rock. Ronald C. Sanders, MD, MS; Katherine Irby, MD.

California: Children's Hospital of Orange County, Orange County. Adam J. Schwarz, MD.

California: Miller Children's & Women's Hospital Long Beach, Long Beach. Christopher J. Babbitt, MD.

California: UCSF Benioff Children's Hospital Oakland, Oakland. Natalie Z. Cvijanovich, MD.

Colorado: Children's Hospital Colorado, Aurora. Aline B. Maddux, MD, MSCS; Peter M. Mourani, MD.

Connecticut: Connecticut Children's, Hartford. Christopher L. Carroll, MD, MS; Robert M. Parker, DO.

Connecticut: Yale New-Haven Children's Hospital, New Haven. John S. Giuliano, Jr., MD; Anjali Gupta, MD.

Florida: Holtz Children's Hospital, Miami. Gwenn E. McLaughlin, MD, MSPH.

Georgia: Children's Healthcare of Atlanta at Egleston and Scottish Rite, Atlanta. Keiko M. Tarquinio, MD; Matthew E. Oster, MD; Preeti Jaggi, MD.

Illinois: Advocate Children's Hospital, Chicago. Vinod Havalad, MD; Stacy Ramsingh, MD.

Illinois: Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago. Kelly N. Michelson, MD, MPH; Bria M. Coates, MD.

Indiana: Riley Hospital for Children, Indianapolis. Courtney M. Rowan, MD, MS.

Kentucky: University of Louisville and Norton Children's Hospital, Louisville. Janice E. Sullivan, MD; Vicki L. Montgomery, MD.

Louisiana: Children's Hospital of New Orleans, New Orleans. Tamara T. Bradford, MD.

Maryland: Johns Hopkins Children's Hospital, Baltimore. Becky J. Riggs, MD.

Maryland: Sinai Hospital of Baltimore, Baltimore. Susan V. Lipton, MD, MPH.

Maryland: University of Maryland Children's Hospital, Baltimore. Ana Lia Graciano, MD.

Massachusetts: Baystate Children's Hospital, Springfield. Kimberly L. Marohn, MD; Rohini S. Harvey, MD.

Massachusetts: Boston Children's Hospital, Boston. Adrienne G. Randolph, MD; Mary Beth F. Son, MD; Jane W. Newburger, MD, MPH; Margaret M. Newhams, MPH; Janet Chou, MD; Lauren A. Henderson, MD, MMSc; Ravi R. Thiagarajan, MBBS, MPH; Olivia Kahn-Boesel, BA.

Massachusetts: Massachusetts General Children's Hospital, Boston. Phoebe H. Yager, MD.

Michigan: Children's Hospital of Michigan, Detroit. Sabrina M. Heidemann, MD; Amarilis A. Martin, MD.

Michigan: University of Michigan CS Mott Children's Hospital, Ann Arbor. Heidi R. Flori, MD, FAAP.

Minnesota: University of Minnesota Masonic Children's Hospital. Janet R. Hume, MD, PhD.

Mississippi: Children's Hospital of Mississippi, Jackson. Charlotte V. Hobbs, MD; Kengo Inagaki, MD; Padma Garg, MD; Roberto P. Santos, MD; Brian Kirmse, MD.

Missouri: Children's Mercy Hospital, Kansas City. Jennifer E. Schuster, MD.

Nebraska: Children's Hospital & Medical Center, Omaha. Russell J. McCulloh, MD; Chelsea Bloom Anderson, MD; Brenda Weidner, MD.

New Jersey: Cooper University Hospital, Camden. Karen S. Walker, MD.

New Jersey: Hackensack University Medical Center, Hackensack. Katharine N. Clouser, MD.

New Jersey: Goryeb Children's Hospital, Morristown. Maria Cecilia Di Pentima, MD; Walter D. Rosenfeld, MD.

New Jersey: Newark Beth Israel Medical Center, Newark. Rowan F. Walsh, MD

New Jersey: Bristol-Myers Squibb Children's Hospital, New Brunswick. Steven M. Horwitz, MD; Lawrence C. Kleinman, MD, MPH, FAAP.

New Jersey: St. Barnabas Medical Center, Livingston. Shira J. Gertz, MD.

New Jersey: The Valley Hospital, Ridgewood. Dennis C. Coffey, MD.

New York: Golisano Children's Hospital, Rochester. Kate G. Ackerman, MD, MPH; Jill M. Cholette, MD.

New York: Kings County Hospital, Brooklyn. Michael A. Keenaghan, MD; Hussam Alharash, MD.

New York: Maimonides Medical Center, Brooklyn. Ariel Daube, MD.

New York: Maria Fareri Children's Hospital, Westchester. Aalok R. Singh, MD, Simon Li, MD, MPH.

New York: The Mount Sinai Hospital, New York City. Sheemon P. Zackai, MD; Jennifer K. Gillen, MD.

New York: Hassenfeld Children's Hospital at NYU Langone, New York. Adam J. Ratner, MD, MPH; Moshe M. Cohn, MD; Philip J. Kahn, MD.

New York: Stony Brook University Hospital, Stony Brook. Ilana Harwayne-Gidansky, MD; Saul R. Hymes, MD.

New York: SUNY Downstate Medical Center University Hospital, Brooklyn. Sule Doymaz, MD.

Ohio: MetroHealth Medical Center, Cleveland. Hulya Bukulmez, MD.

Ohio: University Hospitals Rainbow Babies and Children's Hospital, Cleveland. Amanda Lansell, MD; Steven L. Shein, MD; Amy M. Edwards, MD.

Pennsylvania: Children's Hospital of Philadelphia, Philadelphia. Julie C. Fitzgerald, MD, PhD, MSCE.

Pennsylvania: Penn State Children's Hospital, Hershey. Neal J. Thomas, MD, MSc.

Pennsylvania: St. Christopher's Hospital for Children, Philadelphia. Monica L. Koncicki, MD.

Tennessee: Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville. Natasha B. Halasa, MD, MPH.

Tennessee: Le Bonheur Children's Hospital, Memphis. Dai Kimura, MD, FAAP.

Texas: Texas Children's Hospital, Houston. Laura L. Loftis, MD.

Texas: University of Texas Health Science Center, Houston. Alvaro Coronado Munoz, MD.

Texas: University of Texas Southwestern, Children's Health Medical Center Dallas, Dallas. Cindy Bowens, MD, MSCS; Mia Maamari, MD.

Utah: Primary Children's Hospital, Salt Lake City. Hillary Crandall, MD, PhD.

Washington: Seattle Children's Hospital, Seattle. Lincoln S. Smith, MD; John K. McGuire, MD.

CDC COVID-19 Response Team

(listed in PubMed)

Manish M. Patel, MD, MPH; Leora R. Feldstein, PhD, MSc; Erica Billig Rose, PhD MS; Jennifer P. Collins, MD MSC; Mark W. Tenforde, MD PhD; Michael Wu MPH, Victoria T. Chu MD, Alice Wang PhD, Constance E. Ogokeh MPH, Sara S. Kim MPH, Emily R. Smith MPH, Layne Dorough MPH, Courtney N. Sciarratta MPH, and Eric P. Griggs MPH

SUPPLEMENTARY METHODS & RESULTS

Supplementary Methods:

Pediatric sub-specialists identifying cases for submission included critical care, infectious diseases, rheumatology, hospital medicine, and cardiology specialists. Clinicians at participating sites with knowledge of MIS-C patients abstracted medical records onto a standardized form, and data were entered into Research Electronic Data Capture software (REDCap)¹ hosted at Boston Children's Hospital (BCH) or Centers for Disease Control and Prevention (CDC). Data included patient demographics, underlying health conditions, presenting signs and symptoms, clinical course, laboratory values, diagnostic findings, treatments, complications, and outcomes. Data were deidentified except dates and partial zip codes were included for public health surveillance. We excluded patients who had a laboratory-confirmed bacterial infection or other known conditions that could account for their illness, based on clinical judgement.

We classified patients as obese, either through clinician-diagnosed reporting or based on national reference standards for body mass index (BMI).² We restricted obesity calculations for those aged ≥ 2 years. We considered patients as "previously healthy" if they had no reported underlying conditions. We classified those with clinician-diagnosed or BMI-based obesity as previously healthy unless they had one of the underlying non-obesity medical conditions.

We also assessed KD-like signs and symptoms (Table S2) and report "KD-like features" including bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash, and cervical lymphadenopathy >1.5 centimeter (cm).

Because reference values for troponin vary, we categorized troponin dichotomously as high or normal based on each laboratory's reference range. We chose a cut-off of >400 pg/mL for BNP to account for possible reporting of N-terminal pro B-type natriuretic peptide NT-proBNP.³

This study aims to depict the scope of MIS-C in the initial 2 months, therefore we show descriptive statistics only. Illness day 1 was the first day of reported MIS-C signs and symptoms. We reported days of fever only among patients who were discharged or died.

To assess the temporal relationship between COVID-19 and MIS-C, we defined COVID-19 activity as the percent of respiratory specimens from persons aged <21 years tested for SARS-CoV-2 that were positive. Using test result data reported to CDC through commercial and public health laboratories, we calculated pooled statewide estimates of COVID-19 activity across 25 of 26 states in which a hospital in our system that reported ≥ 1 MIS-C case was located. We compared this pooled statewide COVID-19 activity by date with the distribution of MIS-C hospitalization dates for included cases.

To address duplicate reporting, we excluded 27 patients (2 of these were deaths) included in the New York State Department of Health (NYSDOH) surveillance report.⁴ These patients were identified by the NYSDOH by comparing the case date of hospitalization and date of birth at overlapping hospitals in the *Overcoming COVID-19* and NYSDOH surveillance systems. We compared the demographics, clinical characteristics, and outcomes of patients with multisystem inflammatory syndrome in children (MIS-C), excluding and including the 27 cases at these overlapping centers (Table S8). One additional case that may still be overlapping could not be verified. Of the 186 cases in our series, investigators

have published an additional 5 cases (3%) in 2 reports for their unique clinical presentation. These reports include:

1. A case report that focused on reaction to intravenous immunoglobulin (IVIG) with hypotension in patient with incomplete KD.⁵
2. A case series of 6 patients, 4 of whom are in our report.⁶

Note: Investigators from The Mount Sinai Hospital in New York City published a case-series of four patients with MIS-C.⁷ These four cases were not included in our report and were part of the 27 overlapping cases with NYSDOH surveillance that were removed from our report.

Supplemental Results:

Twenty-one cases were excluded from the analysis based on independent review because they did not meet our case definition: 13 patients had involvement of <2 organ systems, 3 did not have a fever, 1 had a positive blood culture indicating a potential other cause, 1 had no elevated markers of inflammation, 2 had no signs of severe clinical illness based on independent review by 3 clinicians, and 1 was SARS-CoV-2 negative outside of the time window ending May 15.

Patients with laboratory-confirmed SARS-CoV-2 were older (median 9.1 years) than those epidemiologically-linked to COVID-19 cases (median 3.9 years). The majority of patients (n=135, 73%) were reportedly previously healthy and (n=33, 18%) had underlying respiratory conditions, however, among children at least two years of age (n=153), 45 (29%) were obese based on BMI whereas only 12 (8%) had a clinical diagnosis (Table S4). Obesity is not defined in children <2 years old.

Among 186 patients, 70 (38%) were tested by RT-PCR only, 3 (1.6%) by serology alone, 111 (60%) by both RT-PCR and serology, and 2 (1.0%) by neither method. Among 181 tested by RT-PCR, 73 (40%) were positive. Among 131 tested by serology, 85 (65%) were antibody positive. Among 111 tested by RT-PCR and serology, 28 (25%) were negative by both, 55 (50%) were antibody positive and RT-PCR negative, 1 (1%); was RT-PCR positive and antibody negative, and 27 (24%) were positive for both.

A higher proportion of MIS-C patients with laboratory confirmed SARS-CoV-2 infection, compared with epidemiologically linked patients, had involvement of ≥ 4 organ systems (n=101, 77% and n=31, 56%, respectively) Table 1. A higher proportion of patients with laboratory-confirmed SARS-CoV-2 infection, compared with epidemiologically linked cases, required intensive care (n=115, 88% and n=33, 60%, respectively). A higher proportion of patients aged ≥ 5 years required intensive care compared with those aged <5 years (87% and 67%, respectively).

Cardiac: Other common echocardiographic findings were mitral valve regurgitation (n=57, 34%) and pericarditis or pericardial effusion (n=49, 29%). Among patients who received mechanical ventilation, 8% had pulmonary edema secondary to left heart failure documented in their chart. Among all patients, 9 (5%) and 61 (33%) patients had measured or qualitatively assessed ejection fractions of <30% and 30 to <55%, respectively.

Non-cardiac: Other clinical complications included pleural effusions (n=50, 27%), neurologic involvement (n=12, 6%), acute kidney injury (n=10, 5%), and hepatitis (n=10, 5%) (Table S6).

Detection of other viruses: Although nine (5%) patients tested positive for other viruses, we included these after expert adjudication by infectious disease specialists deemed these results were unlikely to explain the clinical presentation or disease severity. Viral test results were as follows: among the patients with RT-PCR confirmation of SARS-CoV-2 infection, additional viral infections included Epstein–Barr virus (1 patient), Epstein–Barr virus plus parvovirus B19 (1 patient), rhinovirus (2 patients), rhinovirus/enterovirus (1 patient), and human metapneumovirus (1 patient). Among the patients who were antibody-positive for SARS-CoV-2 infection, additional viral infections included rhinovirus (1 patient) and parainfluenza (1 patient). Among the patients with an epidemiologic link to a person with COVID-19, additional viral infections included human metapneumovirus (1 patient).

KD-like features of MIS-C: Among all patients with MIS-C, 131/167 (78%) had fever for ≥ 5 days, and 151/167 (90%) had fever for ≥ 4 days. Other than fever, the most common KD-like features in patients with MIS-C were rash (n=110, 59%) and bilateral conjunctival injection (n=103, 55%). Overall, 74 patients (40%) had fever for ≥ 5 days and either 4–5 KD-like features or 2–3 KD-like features with additional laboratory/echocardiographic findings (Table S2, Table 2). Among those with 4–5 KD-like features (n=38), oral mucosal changes, rash, bilateral conjunctival injection, peripheral extremity changes were present in at least 95% of patients; cervical lymphadenopathy >1.5 cm was relatively common (n=7, 18%). Among 36 (19%) patients with 2–3 KD-like features and laboratory or echocardiographic findings, conjunctivitis (n=30, 83%), rash (n=27, 75%), and oral mucosal changes (n=16, 44%) were most common.

Treatment: Overall, 77 (41%) received IVIG and corticosteroids; 67 (36%) patients received IVIG alone. Three patients (2%) received plasma exchange or convalescent plasma.

Table S1: Case definition used in this study for multisystem inflammatory syndrome in children (MIS-C)

Inclusion criteria
<ul style="list-style-type: none"> Fever > 38.0°Cⁱ AND Laboratory evidence of inflammationⁱⁱ AND Evidence of clinically severe hospitalized illness among children aged <21 years with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) AND One of the following: <ol style="list-style-type: none"> SARS-CoV-2 positive RT-PCR test SARS-CoV-2 positive antibody test SARS-CoV-2 negative RT-PCR and antibody tests but with identified COVID exposureⁱⁱⁱ within the four weeks prior to the onset of symptoms
<p>ⁱFever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours</p> <p>ⁱⁱIncluding, but not limited to, one or more of the following: neutrophilia; lymphopenia; hypoalbuminemia; and elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6)</p> <p>ⁱⁱⁱKnown exposure to a person with laboratory-confirmed COVID-19 or a clinical diagnosis of COVID-19 within 4 weeks prior to onset of MIS-C. Patients with hospital admission from March 15 – May 15, 2020 with negative antibody test or no antibody test and unknown exposure were included based on clinician judgment.</p>

Table S2: Kawasaki disease-like (KD-like) signs evaluated in patients with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 illness

Type	Signs
Complete KD	<p>Fever ≥ 5 days* (some experts make the diagnosis with ≥ 3 days of fever) and ≥ 4 of the following 5 criteria:</p> <ul style="list-style-type: none"> • Bilateral conjunctival injection • Oral mucosal changes • Peripheral extremity changes • Rash • Cervical lymphadenopathy >1.5 cm
Incomplete KD	<p>Fever ≥ 5 days AND 2–3 of the following signs OR infants <6 months with fever ≥ 7 days without other explanation:</p> <ul style="list-style-type: none"> • Bilateral conjunctival injection • Oral mucosal changes • Peripheral extremity changes • Rash • Cervical lymphadenopathy >1.5 cm <p>AND CRP ≥ 3.0 mg/dL or ESR ≥ 40 mm/hr</p> <p>AND ≥ 3 of the following laboratory criteria:</p> <ul style="list-style-type: none"> • Anemia for age** • Platelet count of $\geq 450,000$ after the seventh day of fever • Albumin ≤ 3.0 g/dL • WBC count of $\geq 15,000/\text{mm}^3$ • ALT >40 U/L <p>OR</p> <ul style="list-style-type: none"> • Positive echocardiogram**
<p>*Although some experts make the diagnosis with ≥ 3 days of fever, we used fever ≥ 5 days for this analysis.</p> <p>**Anemia for age was defined as any hemoglobin value less than the following values by age:</p> <ul style="list-style-type: none"> • <5 years: 11 g/dL • 5–11 years: 11.5 g/dL • ≥ 12 years: 12 g/dL <p>** Echocardiography was considered positive for purposes of this analysis if any of the following 3 conditions were met:</p> <ul style="list-style-type: none"> • Echocardiography report documenting coronary artery aneurysms • Z score of the LAD or RCA ≥ 2.5 • Presence of 3 other suggestive features: decreased left ventricular function (ejection fraction $<55\%$), mitral regurgitation, z score of LAD or RCA ≥ 2 and < 2.5, and pericarditis/pericardial effusion 	

(Based on available data, these criteria differ slightly from echocardiographic findings used to treat incomplete Kawasaki Disease, which are as follows:

Any of 3 conditions are met: Z score of left anterior descending coronary artery (LAD) or right coronary artery (RCA) ≥ 2.5 ; coronary artery aneurysm is observed; or ≥ 3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or z scores in LAD or RCA of 2 to 2.5).

*McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;135:e927-e99.

Table S3: Definitions used for organ system involvement

Term	Definition (includes any of the listed criteria)
Cardiovascular involvement	<ul style="list-style-type: none"> - Cardiac dysrhythmia or arrhythmia - Ejection fraction <55% - Pulmonary edema due to left heart failure - Coronary artery z score ≥ 2.5 - Pericarditis or pericardial effusion - B-type natriuretic peptide (BNP) >400 pg/mL - Elevated troponin (based on the upper limit of normal for the laboratory running the assay) - Receipt of vasopressor or vasoactive support - Receipt of cardiopulmonary resuscitation (CPR)
Respiratory involvement	<ul style="list-style-type: none"> - Receipt of mechanical ventilation or any type of supplemental oxygen (or increased support for patients receiving respiratory support at baseline) - Severe bronchospasm requiring continuous bronchodilators or - Pulmonary infiltrates on chest radiograph - Lower respiratory infection - Pleural effusion - Pneumothorax or other signs of barotrauma - Pulmonary hemorrhage - Chest-tube or drainage required
Renal involvement	<ul style="list-style-type: none"> - Receipt of dialysis (for patients without chronic renal failure) - Acute kidney injury
Neurologic involvement	<ul style="list-style-type: none"> - Suspected central nervous system infection - Stroke or acute intracranial hemorrhage - Seizures - Coma - Encephalitis, aseptic meningitis, or demyelinating disorder (e.g., acute disseminated encephalomyelitis (ADEM)) diagnosed by a neurologist - Decreased hearing or vision - Iritis or uveitis
Gastrointestinal involvement	<ul style="list-style-type: none"> - Nausea/vomiting - Diarrhea - Abdominal pain - Appendicitis - Pancreatitis - Hepatitis - Gallbladder hydrops or edema
Hematologic involvement	<ul style="list-style-type: none"> - Total white blood cell <4 x10³/μL - Anemia** - Platelet count <150,000 /μL - Deep vein thrombosis - Pulmonary embolism - Hemolysis - Bleeding - Ischemia of an extremity

Mucocutaneous involvement	<ul style="list-style-type: none"> - Bilateral conjunctival injection - Oral mucosal changes - Peripheral extremity changes - Rash or skin ulcers - 'COVID' toes - Swollen red cracked lips - Erythema of palms or soles - Edema of hands or feet - Periungual (nails) desquamation - Conjunctivitis - Peripheral gangrene
Musculoskeletal involvement	<ul style="list-style-type: none"> - Arthritis or arthralgia - Myositis or myalgia
<p>*Acute kidney injury was defined as a creatinine level above the following values by age:</p> <ul style="list-style-type: none"> - <4 weeks: 1.5 mg/dL - 4 weeks—<1 year: 0.6 mg/dL - 1–10 years: 1.05 mg/dL - ≥11 years: >1.5 mg/dL <p>**Anemia was defined as hemoglobin <10 g/dL among children < 1 year of age, otherwise hemoglobin <9 g/dL.</p>	

Table S4: Clinical characteristics of patients with multisystem inflammatory syndrome in children (MIS-C) by age

	Age <5 years (n=66, 35%)	Age 5–12 years (n=75, 40%)	Age 13–20 years (n=45, 24%)	All patients with MIS-C (n=186, 100%)
Previously healthy	55 (83)	51 (68)	29 (64)	135 (73)
Number of organ systems involved				
2	11 (17)	3 (4)	4 (9)	18 (10)
3	16 (24)	14 (19)	6 (13)	36 (19)
4 or more	39 (59)	58 (77)	35 (78)	132 (71)
Types of organ involvement				
Gastrointestinal	60 (91)	70 (93)	41 (91)	171 (92)
Cardiovascular	47 (71)	65 (87)	37 (82)	149 (80)
Hematologic / thrombotic	45 (68)	61 (81)	36 (80)	142 (76)
Mucocutaneous	52 (79)	60 (80)	25 (56)	137 (74)
Respiratory	35 (53)	57 (76)	39 (87)	131 (70)
Musculoskeletal	5 (8)	19 (25)	19 (42)	43 (23)
Renal	2 (3)	7 (9)	6 (13)	15 (8)
Neurologic	3 (5)	4 (5)	5 (11)	12 (6)
Highest level of care				
Ward	22 (33)	10 (13)	6 (13)	38 (20)
ICU without ECMO	43 (65)	64 (85)	33 (73)	140 (75)
ICU with ECMO	1 (2)	1 (1)	6 (13)	8 (4)
Outcome				
Still hospitalized ¹	17 (26)	22 (29)	13 (29)	52 (28)
Discharged alive	49 (74)	52 (69)	29 (64)	130 (70)
Died	0 (0)	1 (1)	3 (7)	4 (2)

¹As of May 20, 2020.

Table S5: Demographic, clinical characteristics, and interventions among patients with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 who died

	Patient 1	Patient 2	Patient 3	Patient 4
Age category	13-20 years	13-20 years	5-12 years	13-20 years
Sex	Female	Male	Male	Female
Race/ethnicity	Black	Black	Black	Hispanic or Latino
BMI-based obesity ¹	Yes	Yes	Yes	Unknown
Clinically documented underlying conditions	None	None	Asthma, clinically-diagnosed obesity	Multiple neurologic conditions
SARS-CoV-2 RT-PCR	Positive	Negative	Positive	Positive
SARS-CoV-2 antibody	Positive	Negative	Not done	Not done
Clinical features prior to/upon admission	Fever, abdominal pain, rhinorrhea, myalgias, loss of taste/smell, mesenteric lymphadenopathy	Fever, nausea, vomiting, abdominal pain, encephalopathy	Fever, nasal congestion, cough, shortness of breath, wheezing, respiratory failure and cardiac arrest	Fever, nausea, vomiting, rhinorrhea, cough, shortness of breath, altered mental status, respiratory failure
Mechanical ventilation	Yes	Yes	Yes	Yes
Mechanical ventilation within 24 hours of admission	No	No	Yes	Yes
Vasopressors	No	Yes	Yes	Yes
ECMO	Yes	Yes	No	Yes
Intravenous immunoglobulin treatment	Yes	No	No	Yes
Corticosteroids treatment	No	Yes	Yes	Yes
Illness day of death ²	13	Unknown	8	12
Hospitalization day of death ³	6	3	1	6

¹BMI-based obesity was defined as BMI >95th percentile for age and sex based on national reference standards (citation)

²Illness day 1 was defined as date of first MIS-C symptoms

³Hospitalization day 1 was defined as date of admission

Table S6: Non-cardiovascular complications laboratory, and diagnostic findings in patients with multisystem inflammatory syndrome in children (MIS-C) by age

	Age <5 years (n=66, 35%)	Age 5–12 years (n=75, 40%)	Age 13–20 years (n=45, 24%)	All patients with MIS-C (n=186, 100%)
Respiratory				
Respiratory insufficiency / failure ¹	21 (32)	50 (67)	38 (84)	109 (59)
High flow nasal cannula	8 (12)	25 (33)	16 (36)	49 (26)
CPAP / BiPAP	4 (6)	17 (23)	11 (24)	32 (17)
Invasive mechanical ventilation	7 (11)	18 (24)	12 (27)	37 (20)
Pleural effusions	6 (9)	28 (37)	16 (36)	50 (27)
Infiltrates on chest X-ray	22 (33)	29 (39)	28 (62)	79 (42)
Gastrointestinal				
Any gastrointestinal symptoms ²	60 (91)	69 (92)	41 (91)	170 (91)
Hepatitis or hepatomegaly	1 (2)	6 (8)	3 (7)	10 (5)
Pancreatitis	0 (0)	5 (7)	1 (2)	6 (3)
Gallbladder hydrops	0 (0)	2 (3)	1 (2)	3 (2)
Appendicitis	0 (0)	2 (3)	0 (0)	2 (1)
Hematologic/thrombotic				
Deep vein thrombosis/pulmonary embolism	0 (0)	1 (1)	3 (7)	4 (2)
Platelets <150,000	28 (42)	41 (55)	32 (73)	101 (55)
Hemoglobin <9 g/dL	35 (53)	42 (56)	11 (25)	88 (48)
Fibrinogen >400 mg/dL	33 (67)	56 (86)	33 (85)	122 (80)
International normalized ratio (INR) >1.1	32 (63)	58 (79)	37 (90)	127 (77)
Musculoskeletal				
Arthritis or arthralgias	0 (0)	3 (4)	1 (2)	4 (2)
Myositis or myalgias	3 (5)	5 (7)	7 (16)	15 (8)
Renal				
Acute kidney injury ³	1 (2)	6 (8)	3 (7)	10 (5)
Renal failure requiring dialysis	1 (2)	1 (1)	4 (9)	6 (3)
Neurologic⁴				
Encephalitis, aseptic meningitis, or demyelinating disorder	1 (2)	2 (3)	1 (2)	4 (2)
Seizures	1 (2)	0 (0)	2 (4)	3 (2)
Coma or unresponsive within 24 hours of admission	0 (0)	1 (1)	2 (4)	3 (2)

¹Defined as requiring any supplemental oxygen²Definitions are in Supplement Table 3³Definition of acute kidney injury in Supplement Table 3.⁴Diagnosed by a neurologist

Table S7: Laboratory value numerators and denominators for *Figure 3: Laboratory markers in patients with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19*

	Age <5 years	Age 5-12 years	Age 13-20 years	Overall
Fibrinogen >400 mg/dL	33/49 (67)	56/65 (86)	33/39 (85)	122/153 (80)
C-Reactive Protein (CRP) ≥3 mg/dL	50/60 (83)	67/70 (96)	39/42 (93)	156/172 (91)
Highest CRP mg/dL, median (IQR)	13.6 (6.8, 19.7)	19.3 (15.6, 29.2)	23.9 (16.3, 29.9)	17.8 (12.8, 25.9)
Albumin ≤3 g/dL	45/64 (70)	62/72 (86)	36/42 (86)	143/178 (80)
Lowest albumin g/dL, median (IQR)	2.6 (2.1, 3.2)	2.3 (2.0, 2.6)	2.7 (2.3, 2.8)	2.5 (2, 2.9)
Ferritin >500 ng/mL	22/52 (42)	47/68 (69)	31/43 (72)	100/163 (61)
Highest ferritin ng/mL, median (IQR)	403 (259.8, 732.5)	679.8 (377.9, 1126.9)	938 (449.0, 1609.2)	639 (332.7, 1178.2)
Lymphocytopenia ¹	39/65 (60)	66/75 (88)	42/44 (95)	147/184 (80)
Neutrophilia ²	37/65 (57)	56/75 (75)	33/44 (75)	126/184 (68)
Hemoglobin <9 g/dL	35/66 (53)	42/75 (56)	11/44 (25)	88/185 (48)
INR >1.1	32/51 (63)	58/73 (79)	37/41 (90)	127/165 (77)
Platelets <150,000	28/66 (42)	41/75 (55)	32/44 (73)	101/185 (55)
Platelets <100,000	17/66 (26)	22/75 (29)	19/44 (43)	58/185 (31)
Lowest platelets cells/mL, median (IQR)	199 (98.5, 320.2)	140 (94, 197.5)	103.5 (80, 154.5)	133 (88, 235)
ESR ≥40 mm/hr	32/44 (73)	39/49 (80)	19/24 (79)	90/117 (77)
Highest ESR mm/hr, median (IQR)	62 (36.8, 88.5)	68 (46, 100)	66.5 (44.2, 84)	65 (42, 91)
Increased troponin ³	16/48 (33)	37/66 (56)	24/39 (62)	77/153 (50)
B-type natriuretic peptide (BNP) >400 pg/mL	27/42 (64)	47/57 (82)	20/29 (69)	94/128 (73)
Highest BNP pg/mL, median (IQR)	646.5 (246.2, 3324.5)	1412 (661, 4626)	1318.5 (357, 14800)	1194.7 (390.8, 4833)
ALT/SGPT ≥40 U/L	33/65 (51)	50/74 (68)	33/43 (77)	116/182 (64)
D-dimer >3000 ng/mL FEU	24/38 (63)	37/54 (69)	18/26 (69)	79/118 (67)
Highest D-dimer ng/mL FEU, median (IQR)	4065 (2240, 8062.5)	4575 (2482, 9998.5)	3980 (1867.5, 6437.5)	4090 (2240, 8404.5)

Table S8: Comparison of demographics, clinical characteristics, and outcomes of patients with multisystem inflammatory syndrome in children (MIS-C), excluding and including the 27 cases at these centers that were included in the New York Department of Health report.

	Patients with MIS-C, excluding those in the New York Department of Health report n=186	Patients with MIS-C, including 27 in the New York Department of Health report n=213
Male	115 (62)	134 (63)
Age, median (IQR)	8.3 (3.3, 12.8)	8.4 (3.6, 12.8)
<1 year	13 (7)	13 (6)
1–4 years	53 (28)	56 (26)
5–9 years	46 (25)	55 (26)
10–14 years	44 (24)	56 (26)
15–20 years	30 (16)	33 (15)
Race and Ethnicity¹		
White, non-Hispanic	35 (19)	38 (18)
Black, non-Hispanic	46 (25)	51 (24)
Other race, non-Hispanic	9 (5)	10 (5)
Unknown	41 (22)	54 (25)
Hispanic or Latino ethnicity	57 (31)	62 (29)
Underlying conditions		
Previously healthy ²	135 (73)	156 (73)
At least one underlying condition	51 (27)	57 (27)
Respiratory	33 (18)	37 (17)
Cardiac	5 (3)	5 (2)
Immunosuppressed or autoimmune	10 (5)	11 (5)
Other condition ³	20 (11)	21 (10)
Clinically-diagnosed obesity ⁴	12/153 (8)	13/186 (7)
SARS-CoV-2 test results		
RT-PCR positive	73 (39)	91 (43)
Antibody positive and RT-PCR negative/unknown	58 (31)	66 (31)
RT-PCR and antibody negative or unknown ⁵	55 (30)	56 (26)
Number of organs involved		
2	18 (10)	19 (9)
3	36 (19)	39 (18)
4 or more	132 (71)	155 (73)
Clinical phenotype		
Kawasaki disease	74 (40)	86 (40)

Kawasaki disease (complete) with no myocardial dysfunction	18 (10)	22 (10)
Kawasaki disease (incomplete) with no myocardial dysfunction	9 (5)	11 (5)
Kawasaki disease (complete or incomplete) and myocardial dysfunction	47 (25)	53 (25)
No Kawasaki disease and myocardial dysfunction	59 (32)	70 (33)
Neither Kawasaki disease nor myocardial dysfunction	53 (28)	57 (27)
Highest level of care		
Ward	38 (20)	41 (19)
ICU - no ECMO	140 (75)	163 (77)
ICU - ECMO	8 (4)	9 (4)
Outcome		
Still hospitalized as of May 20, 2020	52 (28)	56 (26)
Discharged alive	130 (70)	151 (71)
Died in hospital	4 (2)	6 (3)

¹Race categories are not mutually exclusive.

² No reported underlying conditions including clinician-diagnosed or BMI-based obesity ³Includes neurologic, hematologic, gastrointestinal/hepatic, renal, endocrine (including diabetes mellitus), metabolic (other than obesity), and genetic conditions.

⁴Based on reporting by clinicians among those aged ≥ 2 years

⁵Epi-linked refers to patients without laboratory-confirmed SARS-CoV-2 infection (i.e., because of negative or unknown test results or lack of testing) who had exposure to a person with COVID-19 within 4 weeks prior to the onset of MIS-C symptoms.

Supplement References

1. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
2. Centers for Disease Control and Prevention. Available at (https://www.cdc.gov/growthcharts/clinical_charts.htm) /Last accessed May 20, 2020.
3. Rorth R, Jhund PS, Yilmaz MB, et al. Comparison of BNP and NT-proBNP in Patients With Heart Failure and Reduced Ejection Fraction. *Circ Heart Fail* 2020;13:e006541.
4. Dufort et al. NY DOH paper on MIS-C in current NEJM [Place holder for copy-editors].
5. Rivera-Figueroa EI, Santos R, Simpson S, Garg P. Incomplete Kawasaki Disease in a Child with Covid-19. *Indian Pediatr* 2020.
6. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series. *J Pediatric Infect Dis Soc* 2020.
7. Waltuch T, Gill P, Zinns LE, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. *Am J Emerg Med* 2020.